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Design of Potential Inhibitors of *Pf*5-ALAS in Liver Stage *Plasmodium falciparum*: A Sustainable Chemotherapeutic Approach to Address Antimalarial Resistance

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Abstract. *Plasmodium falciparum* delta-aminolevulinate synthase (*Pf*5-ALAS) is the first enzyme in the heme biosynthetic pathway, and it is a liver stage specific enzyme in the developmental stages of *Plasmodium falciparum*. 8-amino quinoline derivatives have been reported to be active against liver stage parasite and hence was used as a template in the design of 12 derivatives as sustainable chemotherapeutics that were screened in this study designed as potential inhibitors of *Pf*5-ALAS. The target was modelled due to the unavailability of its experimentally validated 3-dimensional (3D) structure. The binding energy of all 12 designed compounds ranged from -7.9 to -9.1 Kcal/mol which all performed better than primaquine a known inhibitor of liver stage malaria. All twelve designed compounds had comparatively good pharmacokinetic profiles and did not present a toxicity risk, according to *in silico* ADMET prediction. The position and presence of a functional group that introduces a synergistic impact and subsequently raises the binding energy are highlighted in the qualitative structural assessment of the top three hits. This might pave way to highly economical new antimalarial therapeutic for sustainability health and wellbeing in sub-Saharan Africa and beyond.

Keywords: Antimalarial resistance, Chemoprophylaxis, Liver stage malaria, *Pf*5-ALAS Inhibitors, Qualitative structural assessment.

1. Introduction

The global strategy for the elimination of malaria indicates that based on the complex lifecycle of the parasite, it is possible to prevent and eradicate this disease. One of the susceptible bottlenecks for sustainable therapeutic approaches to prevent malaria is targeting the asymptomatic liver stage (LS) [1]. This provides the possibility for the development of drugs that target new sites, which is relevant considering the current drug resistance map. Enzymes in some biosynthetic pathways have been reported as suitable targets for antimalaria discovery, selective inhibition of these enzymes allows for therapeutic intervention [2]. Merozoite invasion of erythrocytes, sporozoite invasion of hepatocytes, trophozoite growth, hemoglobin metabolism, essential compound biosynthesis, gametocytogenesis, etc. are some of the pathways that have been considered in the development of new antimalarial agents [3]. Malaria liver stage chemoprophylaxis refers to medications that act on the parasite when it invades the hepatocytes to destroy the parasite early in the infectious phase, providing a sustainable approach as this deviates from the norm of most chemotherapeutic targeting the asexual blood stage [4]. Essential pathways in the LS parasite are useful starting points for identifying the physiological targets required in the optimization of drugs that might act as potential inhibitors [5]. According to Oberstallar *et al.* (2020), the mitochondrial pathways maintain significance for antimalarial intervention, and combinatorial therapy with medicines operating synergistically against the same target may be beneficial [6]. The LS parasite has long been recognised to rely on distinct metabolic capacities for the manufacture of heme and fatty acids [5]. Nagaraj *et al.* (2013) reported the importance of heme in *Plasmodium specie* parasite infection stages,the biosynthetic pathway is not limited to the liver stage, since the pathway enzymes are also present in the parasite's blood stage [7]. It was stated that since parasites might not be able to import host-synthesised heme, heme production is necessary for liver-stage development. Goldberg et al. (2017) hypothesise that P. spp. does not depend on heme production during blood-stage infection, supporting their theory that a mechanism for scavenging host-derived heme has been developed by parasite to meet cofactor requirements for mitochondrial cytochromes [8]. Inhibiting parasite enzymes in the heme biosynthesis pathway may therefore give effective prophylaxis against later blood-stage malaria. It is consequently critical to design medications that selectively target parasite enzymes while avoiding the inhibition of essential human enzymes.

The reaction of glycine with succinyl-coenzyme A is catalyzed by an enzyme called delta aminolevulinate synthase (5-ALAS), which is dependent on pyridoxal 5'-phosphate (PLP). Carbon dioxide, coenzyme A, and aminolevulinic acid (ALA) are the products of this reaction. ALA is the common committed precursor of all biological tetrapyrroles, including hemes, chlorophylls, and cobalamins [9]. The heme biosynthesis of the *Plasmodium falciparum* parasite occurs in both the mitochondria and the apicoplast with *Pf*5-ALAS being the first enzyme of the pathway. Nitrogen-containing heterocyclic compounds have been extensively reviewed over the years and their activities are documented to be therapeutically effective in the search for new effective *Plasmodium falciparum* medicine. Quinoline derivatives have been reported to be active chemotherapeutic in search for active compounds against malaria [10].

Primaquine, an 8-amino quinoline derivative, is a therapeutically utilised inhibitor of the plasmodium parasite at the liver stage, it has a very high *in-vitro* IC_{50} (~10 μM) [11]. However, the usage of primaquine has been limited by two factors including its limited oral bioavailability due to fast oxidative deamination to carboxyprimaquine and hemolytic anemia after the development of methemoglobinemia, which is most severe in persons with glucose 6-phosphate dehydrogenase insufficiency [12]. A method for identifying potentially bioactive compounds is virtual screening of biologically active compounds against protein targets. The conventional method for the discovery of bioactive molecules has been reported to be expensive and time-consuming due to the low success rate observed, especially at the later stage of the development process [13]. Virtual screening is one of the strategy that is used to optimize the drug discovery process. Bioinformatics and advances in computer modelling have improved on the process involved in modern drug discovery, enabling virtual screening of biologically active molecules to uncover hits and lead compounds. [14]. Recent advancements in parallel and high-performance computing (HPC) platforms, innovative in-silico methods, and computer-aided drug design (CADD) constitute latest approach for drug discovering [15]. The accuracy of high-throughput virtual screening can be improved using machine learning methods via ligand-based, structure-based, or consensus-based approaches [16]. Hence the aim of this study is to identify potential inhibitors of *Pf*5-ALAS which can serve as malaria prophylaxis using CADD approach, then optimize these compounds to design novel inhibitors with good synthetic accessibility scores and improved pharmacodynamics and pharmacokinetics profiles.

2. Material and Methods

*2.1 Homology modelling of Pf*5-ALAS

3D structure of *Pf*5-ALAS was modelled because its experimental structure is not available in the Protein Data Bank (PDB). The protein ID was retrieved from UniProt Knowledgebase (UniProtKB) with the accession number Q8I4X1. The protein sequence was uploaded to the Robetta server, which generated five 3D models. These models were then compared to the AlphaFold 3D structure. MolProbity and Clash scores from the Swiss Model, ERRAT and VERIFY from the UCLA-DOE LAB – SAVES v6 were used in the selection of the most reliable 3D structure. Low clash score and MolProbity values, an average quality score of almost 91% for ERRAT and at least 80% of the amino acids in the 3D/1D profile should score 0.2 for VERIFY indicates a good model. [17].

2.2 Ligand library preparation

Pharmit server was used to develop a ligand-based pharmacophore model based on the interaction of the 3D-modeled structure of Pf5-ALAS and Primaquine was created [18]. The Key features of ligand used to construct an effective pharmacophore query includes hydrogen bond acceptors, hydrogen bond donors, hydrophobicity, and positive ion features. They were chosen based on the 2D interaction of Primaquine and *Pf*5-ALAS (Figure 1). PubChem and Chembl databases were explored for the search returning a total of 978 compounds. These were downloaded and imported into the OpenBabel pane on the PyRx interface to view and convert these compounds to their corresponding docking format [19].

2.3 Molecular docking and post docking analysis

The binding affinity and inhibition potential of the inhibitors were tested by performing molecular docking studies on the autodock vina window on PyRx interface. Discovery Studio 2021 Client [20] was used in post docking analysis. The top hits' structural representations in relation to the binding affinities were also examined.

2.4 Structure activity relationship of best hit

Structural activity relationship (SAR) profile was generated by analysing the structural representations of the best hits in relation to the binding affinities. SAR is the process of identifying connections between the chemical structures of substances under study and the biological activity brought on by changes to functional groups or substituent locations [21]. The best three hits were subjected to qualitative structural analysis to investigate the scaffolds and functional groups that contributed to the various binding interactions seen in the post-screening analysis.

*2.5 Design of potential inhibitors of Pf*5-ALAS *and Insilico activity prediction of designed inhibitors*

The 8-amino quinoline moiety is the major structural backbone of Primaquine and served as the base of the designed compounds. The moieties and functional group present in the best hits that conferred their interaction with *Pf*5-ALAS hence higher binding affinity was considered and incorporated into the structure of designed novel potential inhibitors of Pf5ALAS. To build a structural activity relationship query, the position of substituent was changed giving rise to 5-aminoquinoline derivatives, also an introduction of heteroatom gave rise to quinoxaline derivatives. A total of twelve (12) compounds were designed and screen against *Pf*5-ALAS.

2.6 In silico ADMET prediction and Qualitative structural assessment

A predictive ADMET study was done to estimate the toxicity profile and pharmacokinetic properties of 12 designed compounds to propose if they can pass as being orally active drugs. ADMETlab and SwissADME was used in profile prediction. The parameters taken into consideration were blood–brain barrier permeants, the AMES toxicity which is an indication of mutagenic potential [22], the quantitative estimate druglikeness (QED) scores an indication of structure complexity based on concept of desirability [23]. The synthetic accessibility score which is a measure of the ease of synthesis of the compounds [24] amongst others.

3. Results and Discussion

*3.1 Structure assessment of the Modelled Pf*5-ALAS

Robetta built five 3D models in all, which were compared against each other to see which of the five performed best before being compared to the model that was obtained from AlphaFold. Robetta_1 with MolProbity score of 3.53 (96th percentile), clash score of 1.52 (95th percentile), ERRAT score of 92.09%, and VERIFY score of 74.13% was selected as the best model (Table 1). Subsequent analysis comparing Robetta_1 with the AlphaFold model revealed that

Robetta_1 was within the acceptable range in terms of MolProbity, ERRAT, and VERIFY score and was thus selected for all screening done within this study.

Table 1: *Pf*5-ALAS 3D structure assessment

Validation Index	Alphafold	Robetta1	Robetta2	Robetta3	Robetta4	Robetta5
Ramachandran Favoured (%)	88.38	95.06	94.59	95.06	94.90	92.83
Ramachandran outliers (%)	5.25	0.96	1.75	0.64	1.27	1.27
Cβ deviation (%)	1.49	0.17	_	0.17	_	0.33
Rotamers outliers	17	_	_	1	_	_
Clash Score	1.82 (99th Percentile)	3.93 (96th Percentile)	3.26 (97th Percentile)	4.98 (94th Percentile)	5.94 (91st Percentile)	6.23 (90th Percentile)
Molprobity Score	1.88 (82nd Percentile)	1.52 (95th Percentile)	1.49 (95th Percentile)	1.60 (92nd Percentile)	1.68 (90th Percentile)	1.80 (85th Percentile)
ERRAT	90.82	92.09	91.12	91.23	93.21	86.93
VERIFY3D (%)	42.38	74.13	69.68	72.22	67.46	70.32

3.2 Ligand library generation

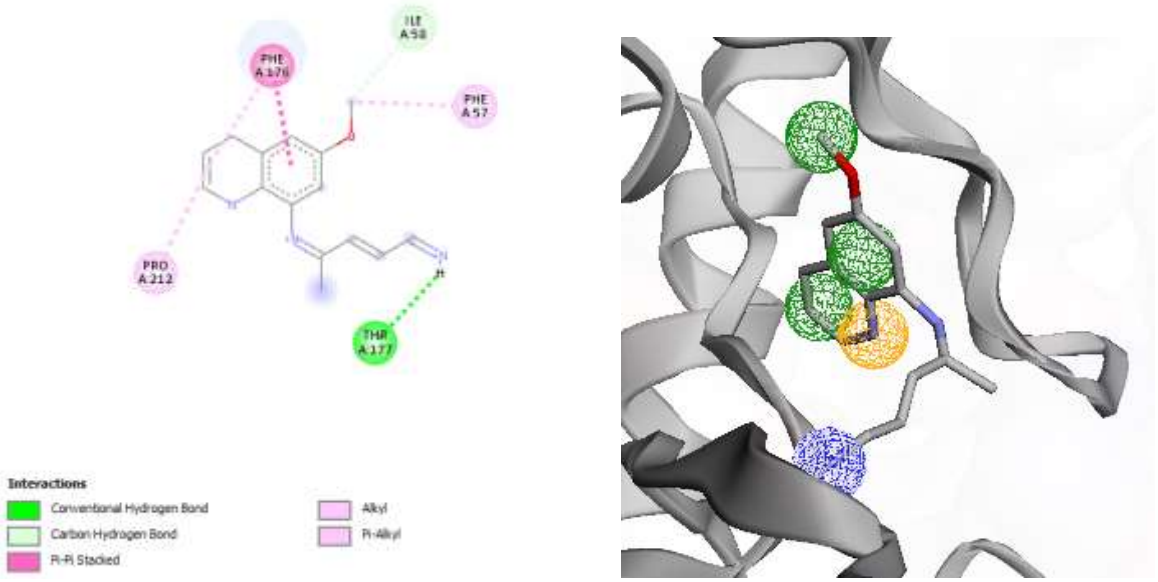


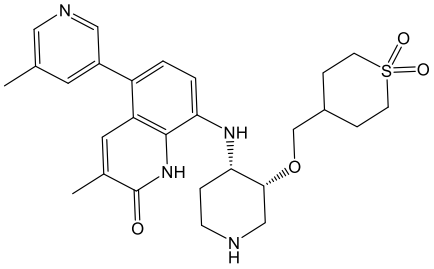
Figure 1: 2D interaction of Primaquine and *Pf*5-ALAS and representative features on pharmit

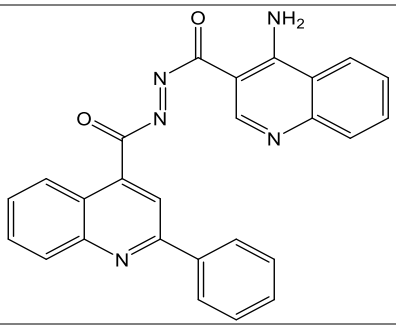
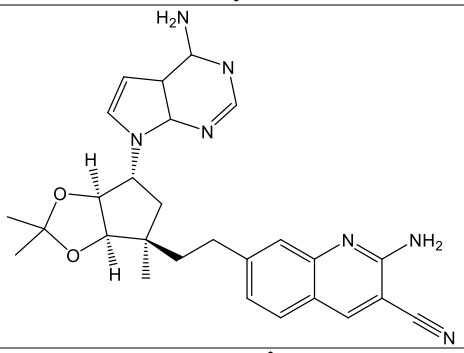
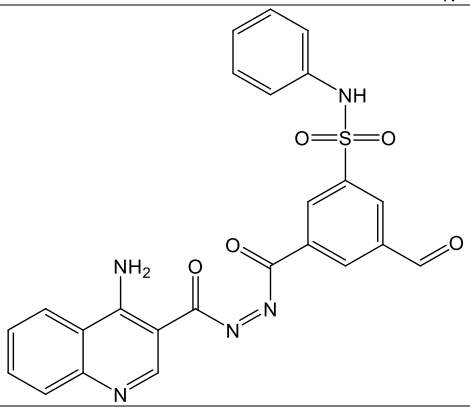
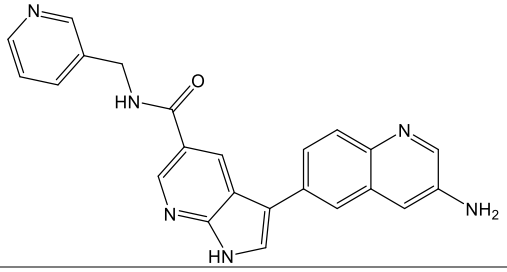
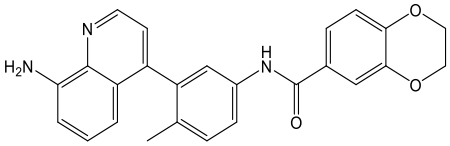
The pharmacophores that were shown to be responsible for the interaction between primaquine and *Pf*5-ALAS are the quinoline moiety, the terminal amine group and ethoxy group. The 2D interaction viewed in discovery studio showed that interaction of the quinoline moeity and target corresponds to the hydrogen acceptor and hydrophobic features, the methoxy group and terminal amine interaction corresponds to hydrophobic and positive ion features respectively on the Pharmit interface (Figure1). These features conferred the interaction and binding affinity of Primaquine and *Pf*5-ALAS, hence were key to search for pharmacophores within the database that had similar features, also taking position of feature into consideration.

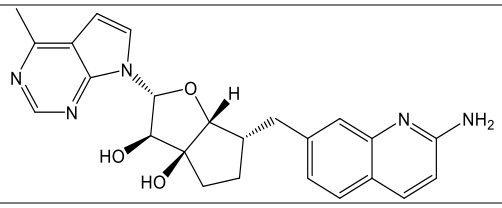
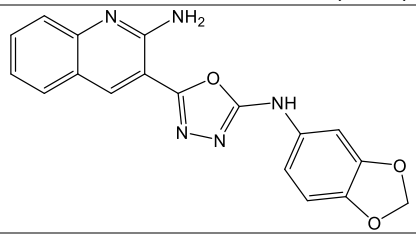
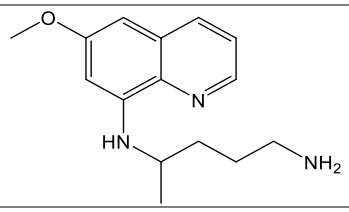
3.3 Molecular docking and Post docking Analyses

Primaquine was one of 979 compounds docked into the *Pf*5-ALAS active site, and the binding energy of the top 8 hits are listed in Table 2. The top 8 hits from the virtual screening had binding affinities that ranged from (-10.6 to -9.3) kcal/mol. Docking score of -6.5 kcal/mol was recorded for Primaquine which is higher than the docking score of the top 8 hits, indicating that they had better binding affinities than primaquine. Compound with code **PubChm122207484** with a docking score of -10.6 kcal/mol, had the best binding affinity. This indicates that this compound is most likely to inhibit *Pf*5-ALAS, acting as a potential malaria prophylaxis Table 1 displays the docking scores of the best hits. The interactions between the atoms of the best hits and the amino acid residues in the Pf5-ALAS active site were viewed and analyzed using the Discovery Studio 2021 interface. Protein ligand complex stability is improved by the intermolecular hydrogen bonds formed between the ligand and the amino acids residue in the active, emphasizing the importance of hydrogen bond donors (HBD) and acceptors (HBA) in the ligand's structure. Interactions comprising alkyl and pi-alkyl, carbon hydrogen bonds, conventional hydrogen bonds, pi-cations, pi-anion, and pi-pi stacking are displayed in the post-screening study. These interactions have a significant impact on each of the best hits' binding affinities and docking scores, the are shown in Figures 2 for PubChm**122207484**, Figures 3 for PubChm**39849065**, and Figure 4 for PubChm**155185182**.Table 2: Binding affinity of 10 best hits from molecular docking of compounds and *Pf*5-ALAS.

Table 2: Binding affinity of 10 best hits from molecular docking of compounds and *Pf*5-ALAS

Compound ID	**3D Structure**	**Docking score (Kcal/mol)**	**nHA**	**nHD**
PubChm122207484		-10.6	6	3

PubChm39849065		-10.2	4	3
PubChm155185182		-10.1	6	2
PubChem39849062		-10	5	4
CHEMBL4788819		-9.9	4	3
CHEMBL3085795		-9.9	4	2

CHEMBL4862596		-9.7	6	3
CHEMBL1087480		-9.3	6	2
Primaquine		-6.5	3	2

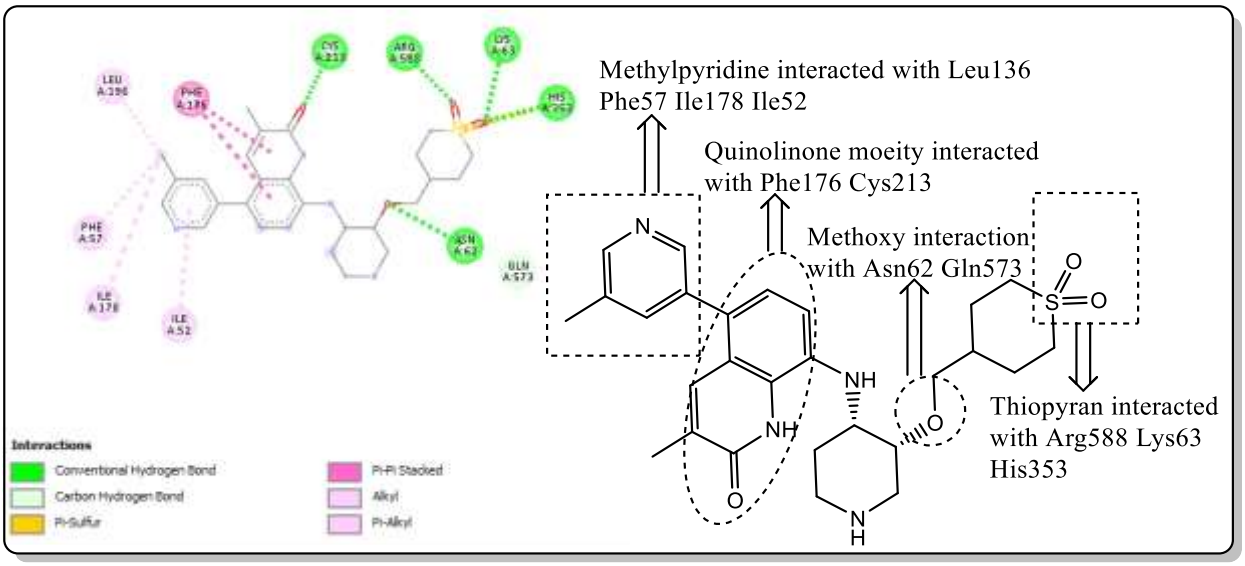


Figure 2: 2D interaction of **PubChm122207484** and active site residue of *Pf*5-ALAS and moieties involved in interaction.

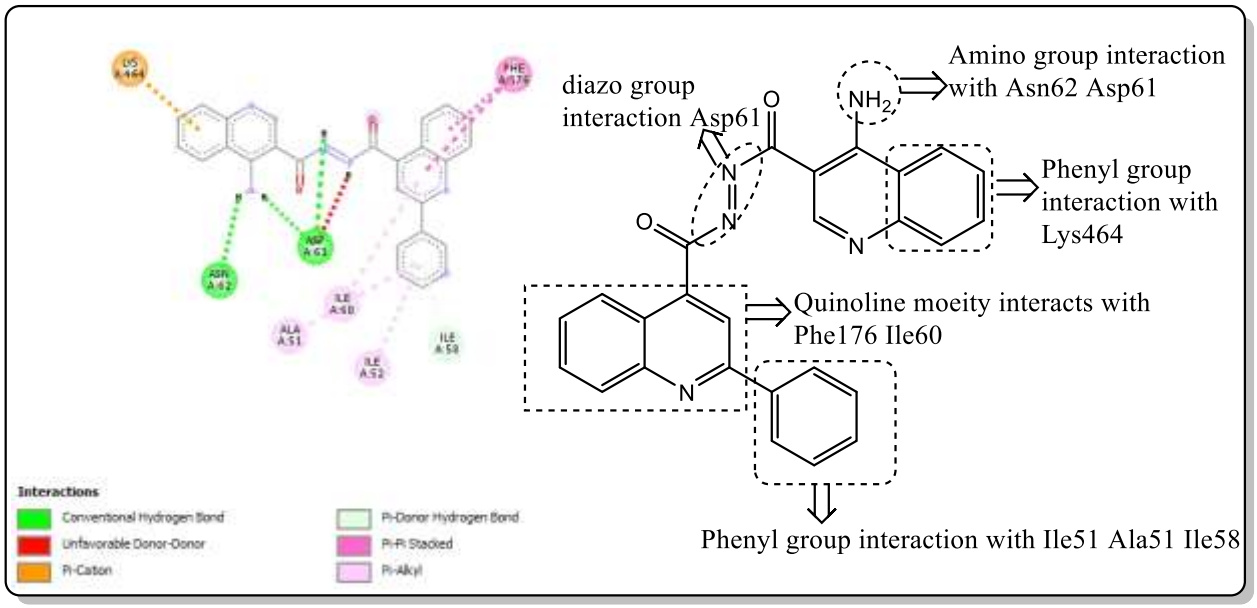


Figure 3: 2D interaction of **PubChm39849065** and active site residue of *Pf*5-ALAS and moieties involved in interaction.

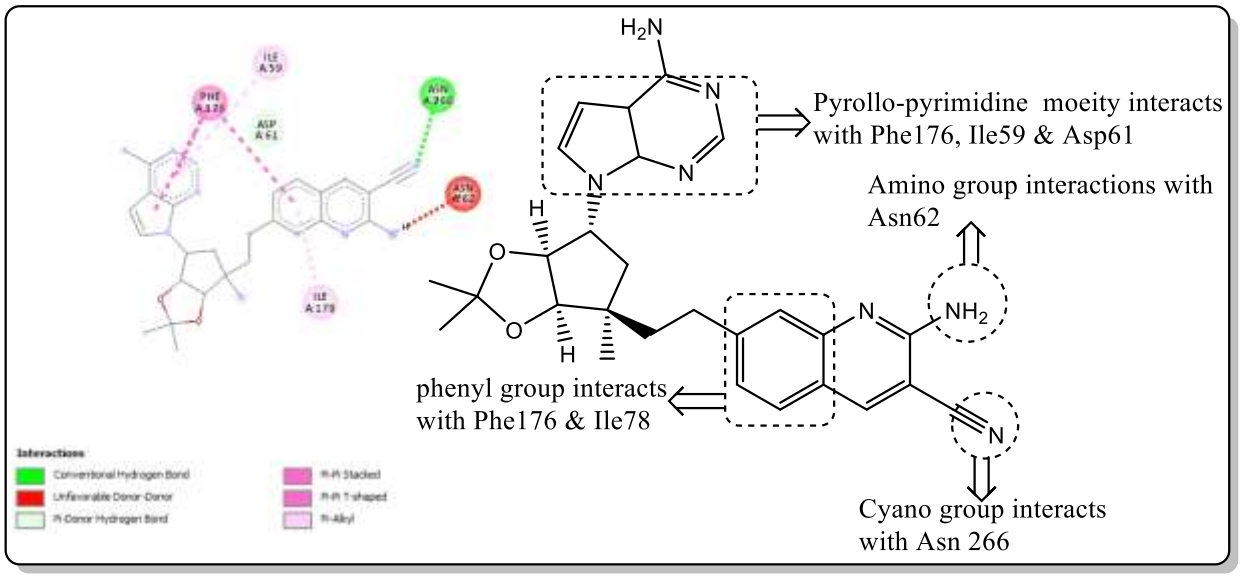


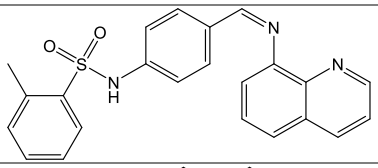
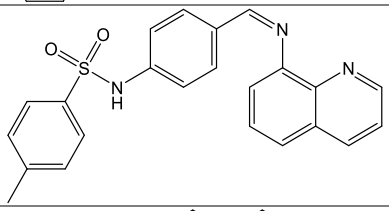
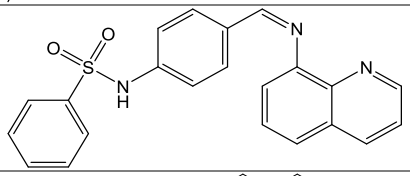
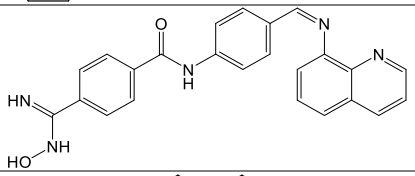
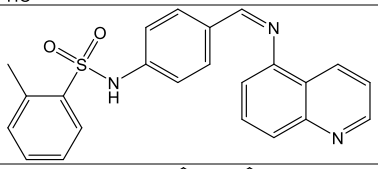
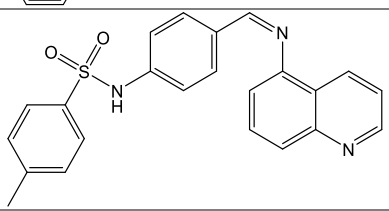
Figure 4: 2D interaction of **PubChm155185182** and active site residue of *Pf*5-ALAS and moieties involved in interaction.

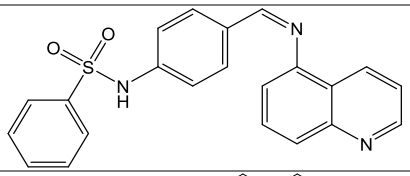
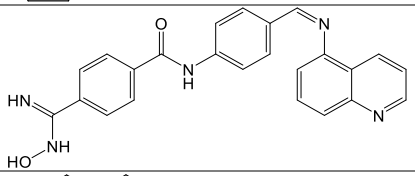
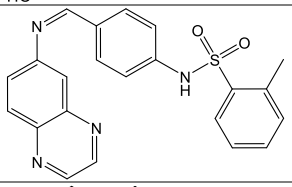
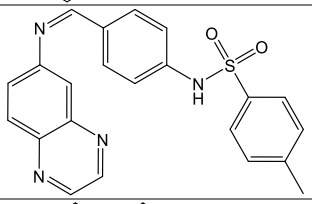
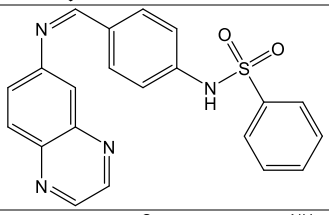
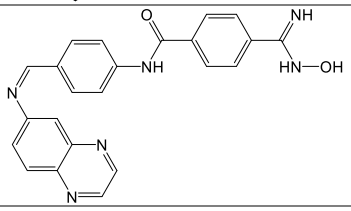
3.4 Structural activity relationship of best hits and design of novel inhibitors of Pf5-ALAS

Functional groups that were involved in the interaction of PubChm**122207484** and *Pf*5-ALAS includes pyridine ring, the quinoline moiety, methoxy group and thiopyran group. The heteroatom, Sulphur, of the thiopyran moiety has 2 carbonyl groups bonded to it (sulphonyl group) and this group contributed 3 conventional hydrogen bonds with amino acid residue Arg588, Lys63 and His353. Ligands with sulphonyl and sulfonamide group have been reported as potent derivatives in the search for active therapeutically active compounds (). Functional group and scaffolds that contributed to the binding affinity of PubChm**39849065** and *Pf*5-

ALAS includes amino group, amido group and the quinoline moiety. The amido group contributed one conventional hydrogen bond with amino acid residue Asp61. The functional group involved in the interaction of PubChm**155185182** and *Pf*5-ALAS are pyrollo-pyrimidine moiety, quinoline scaffold, amino group and nitrile group. The nitrile group interacted via conventional hydrogen bond with amino acid residue Asn266. The functional groups from best hits that were incorporated in the design of the novel inhibitors are sulfonamide group, amido group and nitrile group which can be easily converted to its amidine and amidoxime derivative. This is with the aim of designing compounds that have higher binding affinity than primaquine a known inhibitor of liver stage malaria. A total of 12 compound were designed and docked against *Pf*5-ALAS with their binding energy reported in Table 3.

Table 3: Binding affinity of designed compounds and *Pf*5-ALAS

Compound ID	2D Structure	Docking score (Kcal/mol)	Molecular weight (g/Mol)
1a		-8.5	401.12
1b		-9.1	401.12
1c		-8.3	387.1
1d		-8.2	409.15
2a		-8.4	401.12
2b		-8.8	401.12

2c		-8.2	387.1
2d		-8	409.15
3a		-8	402.12
3b		-8.4	402.12
3c		-8.7	388.1
3d		-7.9	410.15

3.5 In silico ADMET prediction

The pharmacokinetic characteristics and toxicity potential of designed compounds was predicted using AdmetLab shown in Table4. Lipinski's rule of five was introduced as a means of screening since the compounds were designed as good lead compounds in drug discovery. Molecular weight (MW) is considered because drugs with lower MW tend to be dispersed more easily than those with higher MW, hence shoukd be lesser than 500 g/mol [25]. The MWs of the best hits are between 387.1 and 410.15 g/mol, which is within the allowed range. The partition coefficient, clog P value is calculated from the logarithm of between n-octanol and water. Acceptable values are usually Less than 5.0 and values more than 5.0 suggest low hydrophilicity or inadequate absorption [26]. The synthetic accessibility score which is a measure of the ease of synthesis of the compounds was <3 for all the compounds indicating that compounds are easy to synthesise [24]. The TPSA score is a measure of oral bioavailability, with values less than 160 $Å^2$ considered acceptable. All the designed compounds have TPSA score ranging from (71 -125) $Å^2$. The quantitative estimate druglikeness (QED) scores of 9 of

the compounds were predicted to be >0.34 including the best hit, indicating that the structures are not too complex based on concept of desirability. Other properties that were considered indicated the toxicity properties of the designed compounds suggesting their toxicity tendencies to predict drug conformity, compatibility, and safety in vivo. The AMES toxicity, which is an indication of mutagenic potential was low for 9 of the designed compounds. The 3 compounds with high AMES Toxicity potential are derivatives with the amidoxime functional group.

Table 4: ADMET properties of designed compounds

Compound Id	**Medicinal chemistry score**					**Toxicity profile**			
	QED	Synthetic accesibility	TPSA	logP	logS	Skin Sensitivity	AMES	hERG blocker	BBB
1a	0.473	2.209	71.42	4.125	-4.366	0.08	0.193	0.135	0.126
1b	0.473	2.156	71.42	4.22	-4.702	0.081	0.374	0.257	0.076
1c	0.501	2.116	71.42	3.743	-4.514	0.104	0.262	0.254	0.154
1d	0.197	2.297	112.96	2.948	-5.375	0.122	0.94	0.928	0.699
2a	0.473	2.258	71.42	4.26	-4.485	0.073	0.167	0.094	0.101
2b	0.473	2.205	71.42	4.348	-4.961	0.074	0.251	0.187	0.06
2c	0.501	2.166	71.42	3.881	-4.665	0.093	0.189	0.178	0.129
2d	0.197	2.343	112.96	3.095	-5.431	0.113	0.936	0.91	0.72
3a	0.499	2.322	84.31	3.555	-3.97	0.163	0.107	0.467	0.081

3b	0.499	2.269	84.31	3.638	-4.062	0.152	0.221	0.586	0.043
3c	0.52	2.232	84.31	3.17	-3.87	0.203	0.143	0.553	0.08
3d	0.2	2.403	125.85	2.344	-5.037	0.251	0.756	0.929	0.432
Primaquine	0.837	2.634	60.17	2.332	-1.727	0.876	0.888	0.426	0.807

3.6 Qualitative structural assessment using interaction of best 3 hits with Pf5-ALAS

The functional group responsible for the interaction of compound **1b** at the active site of *Pf*5-ALAS includes the imine group, sulfonamide group, methyl benzene moiety and the quinoline moiety (Figure 5). Sulfonamide interaction via conventional hydrogen bond with Asp61 and Asn62, quinoline moiety interacted via alkyl and pi alkyl interaction with Tyr571 and Leu179 and also formed conventional hydrogen bond with Leu179. The methylbenzene moiety interacted via carbon hydrogen bond with Phe176, alkyl and pi-alkyl interaction with Ile59, Tyr210, Phe57 and Pro212 and pi-pi stacking with Phe176. Compound **2b** quinoline moiety interacted via pi-alkyl and alkyl stacking with Cys213, Ile59, pi-pi stacking with Phe176 and carbon hydrogen bond with Phe176. The sulfonamide group interacted with Leu179 via conventional hydrogen bond and Ile178 via carbon hydrogen bond (Figure 6). Compound **3c**, the 3rd best hit is the 6-aminoquinoxaline derivative and interacted with the active site of *Pf*5-ALAS via conventional hydrogen bond and sulfonamide group. This interaction formed with amino acid residue Ile58, Asp61 and Ile60. The Sulfonamide group also interacted with Phe57 via pi-sulfur interaction. The quinoxaline moiety interacted with Ile178 via pi-alkyl bond. The phenyl group interacted via pi-pi stacking and carbon hydrogen bond with Phe176 and pi-sulphur interaction with Cys213 (Figure 7). Compound **1b** had the highest binding affinity and differed in structure from compound **2b** by position of the substituent, compound **1b** being the 5-amino quinoline derivative and **2b** being the 8-amino derivative derivative. This indicated that the position of substituent can introduce a synergistic or antagonistic effect on the activity of drug candidate. Compound **3c** had the quinoline moiety replaced by a quinoxaline moiety and also the methyl on the phenyl is not present for this compound. All three best hits showed similar interaction at the active site of including *Pf*5-ALAS including conventional hydrogen bond, carbonhydrogen bond, pi-pi stacking, pi-alkyl bond, etc. Other interaction were specific to derivative, an example is pi-sulphur interaction observed for compound **3c.**

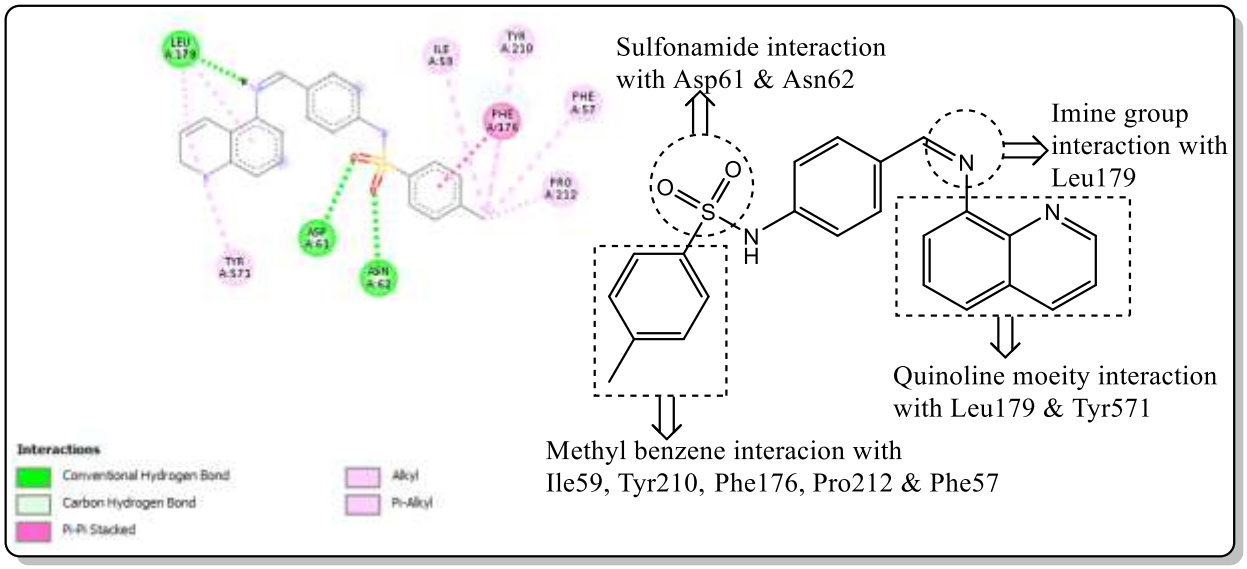


Figure 5: Qualitative structural assessment of Compound **1b**

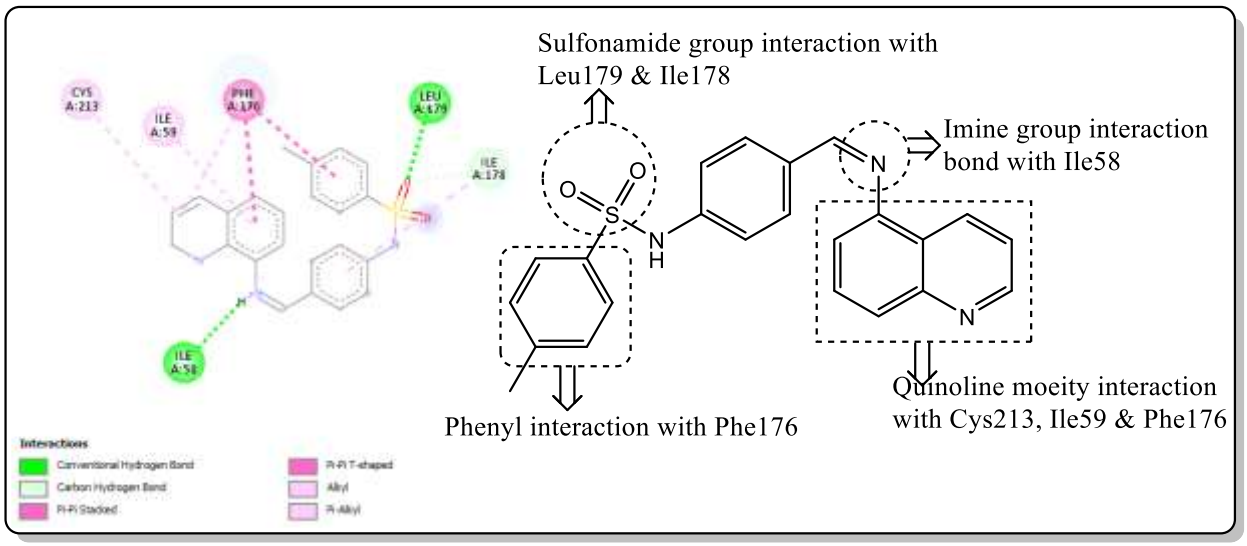


Figure 6: Qualitative structural assessment of Compound **2b**

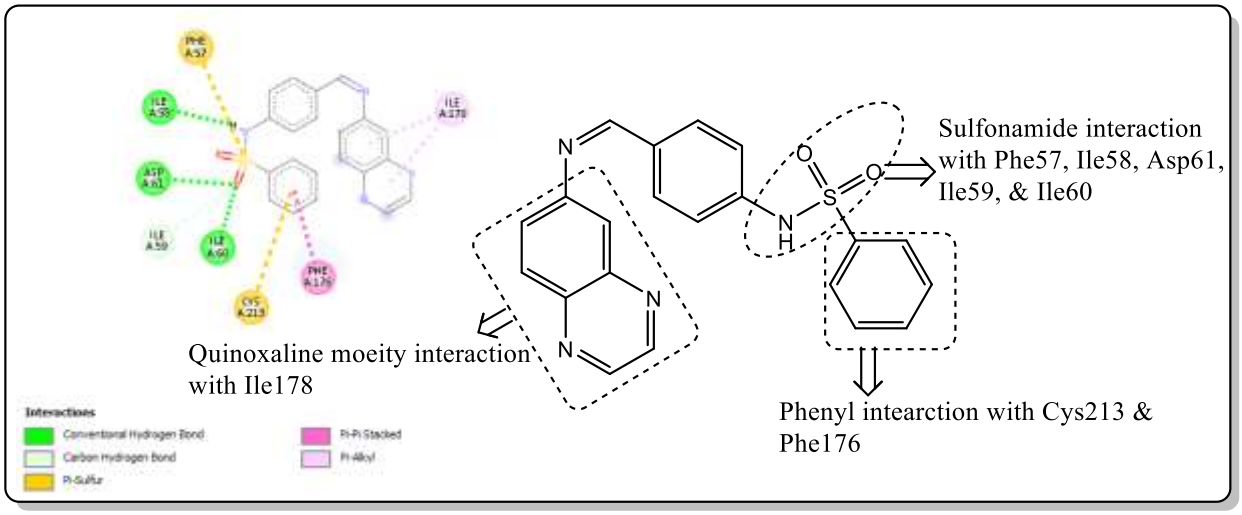


Figure 7: Qualitative structural assessment of Compound **3c**

4. Conclusion and Recommendation

Given the selectivity of *Pf*5-ALAS at the liver stage of parasite growth, it is a promising target for the development of potential malaria chemoprophylaxis. This work provides insight into the design and prediction of possible binding affinities and interaction modes of amino substituted quinoline and quinoxaline compounds, which were designed based on results from virtual screening of primaquine, an approved drug known to be effective against malaria at the liver stage. Among the designed ligands, compounds **1b**, **2b** and **3c** had the highest binding affinities. They also showed good *in silico* ADMET qualities, indicating their safety for synthesis and sustainable development into effective, commercially available chemoprophylaxis. This might pave way to highly economical new antimalarial therapeutic for sustainability health and wellbeing in sub-Saharan Africa and beyond.

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